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09/980,645	03/20/2002	Stefan Anker	101195-64	6782

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	
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05/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,645	ANKER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,17,18,21,25-27 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17,18,21,25-27 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/12/07 has been entered.

2. Claims 1-2, 17-18, 21, 25-27 and 78 are pending and are being acted upon in this Office Action.

3. Claim 27 is objected to because "administered rectally" should have been "**is** administered rectally".

4. The disclosure is objected to because of the word "**ar**sodeoxycholic acid" at page 13, line 8 is misspelled. It should have been "**ur**sodeoxycholic acid".

5. The following are new ground of rejections.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretics, (2) the method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in

combination with a diuretics wherein ursodeoxycholic acid is able to decrease the TNF-α or IL-6 production in the patient in response to endotoxin, (3) the method mentioned above wherein the ursodeoxycholic acid is administered orally, intravenously or rectally, (4) a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretics wherein the ursodeoxycholic acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin, (5) a pharmaceutical formulation comprising ursodeoxycholic acid and a diuretic, **does not** reasonably provide enablement for a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with a diuretics wherein the ursodeoxycholic acid is able to inhibit *any* immune activation in the patients in response to endotoxin, or decrease *any* cytokine production in the patient in response to endotoxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Enablement is not commensurate in scope with claims to the use of ursodeoxycholic acid or ursodeoxycholic acid in combination with diuretics to inhibit any immune activation in any acute or chronic heart failure human patient in response to endotoxin.

The specification discloses only a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising

the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with diuretics. The specification discloses the levels of TNF-α, endotoxin and soluble CD14 are elevated in patient with acute and chronic heart failure, see pages 31-32. The specification at page 45 discloses ursodeoxycholic acid (UCDA) lower LPS stimulated TNF-α in vitro. The specification discloses LPS stimulated TNF-α production I patients with cachexia can be inhibited by UCDA, see spec at page 46.

The specification does not teach administering UCDA to inhibit any immune activation in the patients with acute or chronic hear failure in response to endotoxin. There is no *in vivo* data supporting the claimed as set forth in claim 17. Merely inhibiting TNF-α production and IL-6 production does not resulted in inhibiting the immune activation as a whole. For example, other cytokines production such as IL-1, IL-10, IL-2, IL-12, IL-4, T cell activation, B cell activation, monocyte and macrophage activation have not even been studied using ursodeoxycholic alone, much less a combination of ursodeoxycholic and diuretics in this subpopulation of patient having either acute or chronic heart failure. Given the numerous cell types within the subject, the effect of ursodeoxycholic alone on the immune system as a whole or in combination with any diuretics differ with respect to the type of cells and the interplay among the cells within the subject. Further, the specification does not teach the effective dose of ursodeoxycholic acid alone, let alone the effective dose of a combination of ursodeoxycholic acid (also a diuretic) and any diuretics would be useful for inhibiting immune response as a whole.

Enablement is not commensurate in scope with claims to the use of ursodeoxycholic acid or ursodeoxycholic acid in combination with diuretics to decrease *any* cytokine production in any acute or chronic heart failure in human patient in response to endotoxin. The claim encompasses an unreasonable number of cytokines to be inhibited by ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics.

The specification only two cytokines TNF-α and IL-6 production are inhibited when ursodeoxycholic acid is administered alone to cachectic patient with liver cirrhosis, see page 46.

Other than TNF-α and IL-6 production, the specification does not teach any other cytokine production in response to LPS stimulation could inhibited by administering ursodeoxycholic acid to a patient with acute or chronic heart failure. There are no working example of any cytokines being inhibit by a combination of ursodeoxycholic acid and diuretics.

The art is silent as to which cytokine production could be inhibited by either ursodeoxycholic acid or a combination of ursodeoxycholic acid and diuretics and at what effective doses in patient with acute or chronic heart failure.

Bergamini et al (Hepatology 25(4): 927-933, April 1997; PTO 892) teach LPS stimulated IL-6 and TNF alpha production by human monocytes (see page 930, col. 2, FIG. 3, in particular). In LPS stimulated human monocytes, the addition of UDCA has no effect on IL-6 and TNF-alpha production, see page 929, col. 2, third paragraph, in particular). Bergamini et al further teach ursodeoxycholic acid (UDCA) show modest toxicity to against human monocytes in concentration up to 200μmol/L, see page 931, col. 2, Discussion, in particular). As such, the specification as filed merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 2 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for ameliorating or treating endotoxin-mediated TNF-α production in acute or chronic heart failure in a human wherein the heart failure is "due to *cardiomyopathy of unknown reason, corner artery disease, valvular disease, hypertropic obstructive cardiomyopathy, viral myocarditis, or genetic cardiomyopathy or dilated cardiomyopathy*", (2) the method for ameliorating or treating endotoxin-mediated TNF-α production wherein ursodoxycholic acid is able to *inhibit any*

immune activation in the patients in response to endotoxin, and (3) the method for ameliorating or treating endotoxin-mediated TNF-α production wherein ursodoxycholic acid is able to decrease any cytokine production in the patient in response to endotoxin.

With respect to item (1), the specification at page 6 discloses the following classes of patients in particular may be from treatment 1. Patients with acute heart failure (decompensated chronic heart failure, myocardial infarction). 2. Any decompensated heart failure patients with evidence of peripheral oedema. 3. Patients with severe heart failure (NYHA class III or IV) or with cardiac cachexia. 4. Stable CHF patients if any deterioration occurs, for example patients with a history of decompensation phases. It is preferred that the patient has peripheral and/or bowel oedema.

The specification does not disclose any patient with acute or chronic failure "due to *cardiomyopathy of unknown reason, corner artery disease, valvular disease, hypertropic obstructive cardiomyopathy, viral myocarditis, or genetic cardiomyopathy or dilated cardiomyopathy*" as now claimed. **This is new matter.**

With respect to item (2), the specification does not adequately describe the use of ursodeoxycholic acid or ursodeoxycholic acid in combination with any diuretics to inhibit *any* immune activation in any acute or chronic heart failure in human patient in response to endotoxin.

The specification discloses only a method of ameliorating or treating endotoxin-mediated TNF-α production in acute and chronic heart failure in a human patient, the method comprising the steps of measuring the level of TNF-α, endotoxin or soluble CD14 in the blood of a human patient and if any such level is elected, administering to the patient a therapeutically effective amount of ursodeoxycholic acid or ursodeoxycholic acid in combination with diuretics. The specification discloses the levels of TNF-α, endotoxin and soluble CD14 are elevated in patient with acute and chronic heart failure, see specification at pages 31-32. The specification at page 45 discloses ursodeoxycholic acid (UCDA) lower LPS stimulated TNF-α in vitro. The specification discloses LPS stimulated TNF-α production I patients with cachexia can be inhibited by UCDA, see spec at page 46.

The specification does not describe administering UCDA inhibit *any* immune activation in the patients with acute or chronic hear failure in response to endotoxin. There are no *in vivo* data supporting the claimed as set forth in claim 17. Merely inhibiting TNF-α production and IL-6 production does not result in inhibiting the immune activation as a whole. For example, other cytokines production such as IL-1, IL-10, IL-2, IL-12, IL-4, T cell activation, B cell activation,

monocyte and macrophage activation have not even been studied using ursodeoxycholic alone, much less a combination of ursodeoxycholic and diuretics in this subpopulation of patient having either acute or chronic heart failure. Given the numerous cell types within the subject, the effect of ursodeoxycholic alone on the immune system as a whole or in combination with any diuretics differ with respect to the type of cells and the interplay among the different cell types within the subject is not adequately described. Further, the specification does not disclose the effective dose of ursodeoxycholic acid alone, much less the effective dose of a combination of ursodeoxycholic acid (also a diuretic) and any diuretics that would be useful for inhibiting immune response as a whole in human patients with either acute or chronic heart failure.

With respect to item (3), the claim encompasses an unreasonable number of cytokines to be inhibited by ursodeoxycholic acid or a combination of ursodeoxycholic acid (a diuretic itself) and other diuretics for the claimed method.

The specification only two cytokines TNF-α and IL-6 production are inhibited when ursodeoxycholic acid is administered alone to cachectic patient with *liver cirrhosis*, see page 46.

Other than TNF-α and IL-6 production, there is no disclosure of any other cytokine production in response to LPS stimulation could inhibited by administering ursodeoxycholic acid to a patient with acute or chronic heart failure.

Bergamini et al (Hepatology 25(4): 927-933, April 1997; PTO 892) teach LPS stimulated IL-6 and TNF alpha production by human monocytes (see page 930, col. 2, FIG. 3, in particular). In LPS stimulated human monocytes, the addition of UDCA has no effect on IL-6 and TNF-alpha production, see page 929, col. 2, third paragraph, in particular). Bergamini et al further teach ursodeoxycholic acid (UDCA) show modest toxicity to against human monocytes in concentration up to 200μmol/L, see page 931, col. 2, Discussion, in particular).

With the exception of the specific cytokine TNF-α and IL-6 production are inhibited by administering ursodeoxycholic acid in patient with cahexia for the claimed method, there is insufficient written description about any other cytokine production or immune stimulation in response to endotoxin for the claimed method. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of cytokines and immune activation to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 78 is rejected under 35 U.S.C. 102(b) as being anticipated by Larghi et al (Aliment Pharmacol Ther 11(2): 409-14, April 1997; PTO 892).

Larghi et al *et al* teach a formulation comprising diuretics such as ursodeoxycholic acid and tauro-ursodeoxycholic acid (see entire document, abstract, page 410, col. 1, last paragraph, in particular). A composition is a composition, irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-2, 17-18, are 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anker et al (Am J Cardiology 79: 1426-1430, 1997; PTO 1449) in view of US 5,674,855 (of record, Oct 7, 1997; PTO 892) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892).

Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy exhibit immune activation as measured by a significant elevated level of soluble CD14 receptor (LPS receptor) as compared to control, see page 1427, Table 1, Figure 2, in particular), especially in those with cachexia. These CHF patients also have an increase levels of TNF-α due to endotoxin (LPS) interacting with monocytes, see page 1428, col. 2, second paragraph, in particular). Anker et al teach a method detecting the levels of TNF-α and soluble CD14 using commercially available ELISA test kits, see page 1427, col. 1, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the method for ameliorating or treating endoteoxin-mediated TNF-α production in acute or chronic heart failure in a human by administering ursoedoxycholic acid if any of the TNF-α, soluble CD14 or LPS is elevated.

The invention in claim 25 differs from the teachings of the reference only in that method wherein the bile acid is administered orally.

The invention in claim 27 differs from the teachings of the reference only in that the method wherein the bile acid is administered rectally.

The '855 patent teaches a method of treating endotoxin LPS mediated immune activation such as TNF-α production (inflammatory cytokine production) by administering to a subject such as a human (see col. 9, line 44, in particular) a therapeutically effective amount of ursodeoxycholic acid (see col. 6, line 38-41, col. 7, lines 47-49, col. 8, lines 1-7, col. 8, lines 31-34, col. 9, lines 14-21, in particular). The '855 patent teaches the invention and composition are useful in treating endotoxemia (see col. 11, lines 1-2, in particular). The reference ursodeoxycholic acid can be administered alone or in combination with other phospholipid (see col. 9, lines 57-67, in particular). The reference ursodeoxycholic acid is administered intravenously (see col. 8, line 39, in particular).

Gennaro et al teach oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) and rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics (see page

710, paragraph bridging col. 1 and 2, in particular). The route of administration such as rectally, or orally is within the purview of one of ordinary skill in the pharmaceutical art as taught by Gennaro et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a human subject having chronic heart failure with elevated TNF-α production or soluble CD14 receptor as taught by Anker et al a therapeutically effective amount of ursodeoxycholic acid alone via intravenously as taught by the '855 patent or is administered orally or rectally as taught by Gennaro et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because oral route is the most convenient route for access to the systemic circulation (see page 710, col. 1, last paragraph, in particular) while rectal route is used quite frequently in and important ways of administrating a drug in pediatrics and geriatrics as taught by Gennaro et al (see page 710, paragraph bridging col. 1 and 2, in particular). The route of administration is within the purview of one of ordinary skill in the pharmaceutical art. One having ordinary skill in the art would have been motivated to do administer ursodeoxycholic acid as a method of treating endotoxin-mediated immune activation because the '855 patent teaches ursodeoxycholic acid is useful in treating endotoxemia by inhibiting inflammatory cytokine TNF-α production caused by LPS (see col. 11, lines 1-2, in particular). Anker et al teach human patients with chronic heart failure (CHF) such as idiopathic dilated cardiomyopathy has significant elevated level of soluble CD14 receptor (LPS receptor) or TNF-α due to endotoxin (LPS) (see entire document, see page 1427, Table 1, Figure 2, page 1428, col. 2, second paragraph, in particular).

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anker et al (Am J Cardiology 79: 1426-1430, 1997; PTO 1449) in view of US 5,674,855 (of record, Oct 7, 1997; PTO 892) and Gennaro et al (of record, in Remington: The science and practice of Pharmacy, pages 710-713, Mach publishing company, Eston, Pennsylvania 18042, 1995; PTO 892) as applied to claims 1-2, 17-18, are 25-27 mentioned above and further in view of

The combined teachings of Anker et al, the '855 patent, and Gennaro et al have been discussed supra.

The claimed invention in claim 21 differs from the combined teachings of the references only in that the method for ameliorating or treating endoteoxin-mediated TNF-α production in acute or chronic heart failure in a human by administering ursodeoxycholic acid wherein the ursodeoxycholic acid is able to reduce the permeability of the gut wall to bacteria and/or endotoxin (lipopolysaccharide, LPS).

Schwarzenberg et al teach LPS can cross the intestinal barrier (gut wall) and administration of ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels (see abstract, in particular). Schwarzenberg et al teach UDCA administered prophylactically might reduce the morbidity in clinical conditions leading to gut-derived endotoxemia (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a human subject having chronic heart failure with elevated TNF-α production or soluble CD14 receptor as taught by Anker et al a therapeutically effective amount of ursodeoxycholic acid as taught by the '855 patent or Schwarzenberg et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

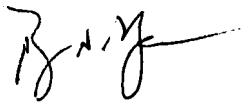
One having ordinary skill in the art would have been motivated to do this because ursodeoxycholic acid (UDCA) can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels as taught by Schwarzenberg et al (see abstract, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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May 11, 2007